## Appendix 3: Supplementary tables [posted as supplied by author]

Table A. Characteristics of Included Randomised or Quasi-Randomised Controlled Trials.

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Akerblom, 2005 [1] Knip, 2010 [2] (Nutramigen, Mead Johnson)	RCT	122/ 120	Finland	TRIGR pilot. Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7, 8, 10	Diabetes Mellitus (clinical diagnosis, autoantibodies)
Becker, 2004 [3]; Chan- Yeung, 2000 [4]; Chan- Yeung 2005 [5]; Wong, 2013 [6] (Good Start, Nestlé)	RCT	281/ 268	Canada	CAPPS Study. Infants with family history of allergic conditions. High risk.	Multifaceted intervention including pHF-whey up to 12 months (only 8.3% of infants used), vs usual care/standard formula.	1, 7	Allergic Sensitisation (SPT), Allergic Rhinitis (DD), Wheeze (ISAAC and modified ECRHS), Eczema (DD), bronchial hyper-responsiveness (Metacholine PC20 <7.8), Lung function (FEV1)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Boyle 2015 [7] (pHF, Nutricia)	RCT	432/431	Australia Singapore England and Ireland	PATCH Study. Term infants with ≥one parent with allergic disease, and formula introduction <18 weeks. High risk.	pHF-whey + prebiotic, vs standard formula, from <18 to 26 weeks. Outcome reported for those starting <4 wks.	1	AD (Hanifin and Rajka criteria)
Chan, 2002 [8] (NanHA, Nestlé)	RCT	76/77	Singapore	Infants whose parents didn't intend to breastfeed/ atopy in a 1st degree relative. High risk.	pHF-whey from birth to ≥4 months, vs standard formula.	0.3, 1, 2, 2.5	Wheeze (DD), Eczema (clinical diagnosis), Allergic Sensitisation (sIgE)
Chirico, 1997 [9] (Vivena HA, Plada)	RCT	Unclear. 21/14 assessed at 6 months	Italy	Very early formula introduction.  Maternal history of atopy.  High risk.	pHF-whey from birth to 6 months vs standard formula.	0.5	Allergic Sensitisation (sIgE), Eczema (clinical diagnosis)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
de Seta, 1994 [10] (Nidina HA, Nestlé)	RCT	Unclear. 23/39 assessed at 2 years	Italy	Representative population of high risk infants. High risk.	pHF-whey with advice to delay CM introduction, vs standard formula from birth to 6 months.	2	Eczema (Hanifin and Rajka criteria), Wheeze (DD)
Dupont, 2009 [11] (Formula unknown)	RCT	138/141	France	Multicentre study of high risk infants. High risk.	eHF vs pHF	1	Total IgE
Halken, 1993 [12] (Nutramigen, Mead Johnson; Profylac, ALK)	RCT	59/62	Denmark	High risk infants with raised cord blood IgE. High risk.	eHF-casein vs eHF- whey, as needed to 6 months.	1.5	Eczema (DD), Wheeze (≥2 physician diagnosed episodes), Food allergy CM (food challenge)
Knip, 2014 [13] (Nutramigen, Mead Johnson)	RCT	2613/2543	Finland	TRIGR study. Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7	Diabetes Mellitus (>=2 or >=1 autoantibodies)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Lovegrove, 1994 [14] (Peptijunior, Nutricia)	RCT	12/14	UK	Allergic pregnant women aged 31 ± 5 years recruited.  High risk.	Multifaceted intervention including eHF-whey vs standard formula/no intervention.	0.5, 1, 1.5	Eczema (DD)
Lowe, 2011 [15] (NanHA, Nestlé)	RCT	206/206	Australia	Representative population.1st degree relative with atopy. High Risk.	pHF-whey vs standard formula during first year.	0.5, 1, 2,	Eczema (DD), Allergic Rhinitis (parental report/DD), Food Allergy (parent report), Wheeze (DD), Allergic Sensitisation (SPT)
Mallet, 1992 [16] (Pregestimil, Mead Johnson)	RCT	92/85	France	Immediate family history of atopy. High Risk.	eHF-casein vs standard formula up to 4 months as needed.	0.33, 1, 2, 4	Wheeze (physician assessment), Eczema (physician assessment), Allergic Sensitisation (sIgE), Food Allergy (parent report)
Marini, 1996 [17] (Nidina HA, Nestlé)	RCT	80/75	Italy	Representative population. High Risk.	pHF-whey vs standard formula up to 5 months as needed.	1, 2, 3	Eczema (DD), Wheeze (≥3 physician diagnosed eposides), Allergic Rhinoconjunctivitis (≥3 consecutive weeks of clinical symptoms)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Martikainen, 1996 [18]; Vaarala,1998 [19] (Nutramigen, Mead Johnson)	RCT	10/10	Finland	Infants of mothers with diabetes. High Risk.	eHF-c vs standard formula, from < 6 until 9 months as needed.	0.5, 1	Diabetes Mellitus (clinical diagnosis, autoantibodies), Food Allergy
Moran, 1992 [20] (pHF, Mead Johnson)	RCT	Unclear. 72/65 assessed at 8 months	USA	Term infants of mothers who elected not to breast feed. Mainly urban middle class families. Normal Risk.	pHF vs standard formula, until 8 months.	0.67	Allergic Sensitisation (sIgE)
Odelram, 1996 [21] (Profylac, ALK)	RCT	~41/ ~41	Finland/ Sweden	Family history of atopy and raised cord blood IgE. High Risk.	eHFvs standard formula for the first year, as needed.	1.5	Food Allergy (physician assessment), Allergic Sensitisation (SPT, sIgE), Eczema (Seymour criteria), Allergic Rhinitis, Wheeze (≥2 physician diagnosed episodes)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Oldaeus,1997 [22]; Oldaeus, 1999 [23] (pHF or Nutramigen, both Mead Johnson)	RCT	51 pHF; 55 eHF; 49 CM	Sweden	Family history of atopy, raised cord blood IgE, maternal/infant milk/egg/fish exclusion. High Risk.	pHF or eHF-casein vs standard formula, from weaning until 9 months.	0.75, 1, 1.5	Eczema (Seymour criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy (open food challenge), Wheeze (≥3 physician diagnosed episodes), Allergic Sensitisation (sIgE, SPT), Wheeze (parent reported)
Paronen, 2000 [24] (Nutramigen, Mead Johnson)	RCT	61/58	Finland	Newborn infants with 1st degree relative with TIDM, and high risk HLA type. High Risk.	eHF-casein vs standard formula, from <6 to 6-8 months as needed. Mean 4.8 months control/ 3.6 eHF.	2	Diabetes Mellitus (autoantibodies)
Porch, 1998 [25] (Good Start, Nestlé; Nutramigen, Mead Johnson)	RCT	59/48	USA	Formula fed from birth. At least one parent with allergy. High Risk.	pHF-whey vs eHF- casein for 1 year.	1	Eczema (DD/nurse diagnosed)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Scalabrin, 2009 [26]; Scalabrin, 2014 [27] (pHF or Nutramigen, both Mead Johnson)	RCT	95/95	USA	Solely formula fed for ≥24 hours prior to 14 days age. Normal risk.	eHF-casein plus LGG vs pHF with LGG, from <14 to 120-150 days.	0.4, 5	Allergic Sensitisation (sIgE-CM), Eczema (DD), Wheeze (DD), Allergic Rhinitis (DD), Food Allergy (DD)
Schmitz, 1992 [28] (Nidal HA, Nestlé)	RCT	128/128	France	Representative population. Normal risk.	pHF-whey vs standard formula for the first 5 days.	0.25, 0.4, 1	Eczema (DD), Allergic Rhinitis (DD), Allergic Sensitisation (sIgE), Wheeze (DD)
Schonberger, 2005 [29] (Nutrilon Pepti, Nutricia)	RCT	242/234	Nether- lands	PREVASC Study.  Mothers with family history of asthma.  High Risk.	Multifaceted intervention including eHF-whey vs standard formula to 6 months.	2	Eczema (ICHPPC), Wheeze (Dutch Guideline "Asthma in Children" and ISAAC), Allergic Sensitisation (sIgE)
Shao, 2006 [30] (Formula unknown)	RCT	23/23	China	Infants with family history of atopy. High Risk.	Multifaceted intervention including pHF-whey vs standard formula, from birth to 12 months.	1.5	Eczema (Wolkerstorfer score), Allergic Sensitisation (SPT)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Tsai, 1991 [31] (NanHA, Nestlé)	RCT	15/18	Taiwan	Healthy term infants at risk of allergy. High Risk.	pHF-wheyfrom 1-2 to 6 months vs standard formula.	1	Eczema (clinical symptoms), Allergic Rhinitis (clinical symptoms), Wheeze, Allergic Sensitisation (sIgE)
Vaarala, 2012 [32] (Peptidi- Tutteli, Valio)	RCT	350/389	Finland	FINDIA Study. Term infants with high risk HLA-type but no maternal diabetes. High risk.	eHF-whey vs standard formula from birth to 6 months as needed.	0.25, 0.5, 3, 6	Diabetes (autoantibodies, clinical diagnosis)
Vandenplas 1992 [33]; Vandenplas 1995 [34] (NanHA, Nestlé)	RCT	~38/~38	Belgium	Family history of atopy, and not breast fed. High Risk.	pHF-wheyvs standard formula, from birth to 6 months.	0.5, 1, 3	Eczema, Allergic Rhinoconjunctivitis (clinical symptoms), Wheeze (clinical symptoms), Allergic Sensitisation (sIgE, SPT), Food Allergy

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
von Berg 2003 [35], 2008 [36], 2010 [37], 2013 [38] (BebaHA, Nestlé; Nutramigen, Mead Johnson; Hipp HA, Nutricia)	RCT	eHF-w 559; eHF- c 580; pHF-w 557; CM 556	Germany	GINI Study. First degree family member with allergic disease. Representative population. High Risk.	pHF-whey, eHF-caseinor eHF-whey vs standard formula to 6 months as needed. 65% introduced formula <4 weeks.	1, 3, 6, 10	Eczema (Hanifin and Rajka criteria), Food Allergy - Any (IgE and non- IgE, clinical symptoms), Wheeze (parent reported ≥3 episodes), Allergic Sensitisation (sIgE)
Zeiger 1989 [39], 1995 [40] (Nutramigen, Mead Johnson)	RCT	Unclear. 103/185 followed at 4 months	USA	Infants covered by Kaiser Permanente Health Plan, with an allergic parent. High Risk.	Multifaceted intervention including eHF-casein , vs no intervention/standard formula to 1 year.	2, 4, 7	Eczema (Hanifin and Rajka Criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy - Any (DD), Wheeze (≥2 physician diagnosed episodes), Allergic Sensitisation (SPT)
Exl, 1998 [41] (Beba HA, Nestlé)	qRCT	564/ 566	Switzerla nd.	ZUFF Study. Representative population. Normal risk.	pHF-whey with solid foods delayed to 4 months, vs standard care.	0.1, 0.25, 0.5	Eczema (parental monitoring and DD), Wheeze

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Halken, 2000 [42] (NanHA, Nestlé)	qRCT	pHF 85; eHF-w 82; eHF-c 79	Denmark	High risk infants with raised cord blood IgE. High risk.	pHF-whey vs eHF-casein or eHF-whey from birth to 4 months as needed.	1.5	Wheeze (≥3 physician diagnosed episodes), Eczema (DD), Allergic Rhinoconjunctivitis (DD), Food Allergy (Parental report/challenge)
Juvonen, 1994 [43]; Juvonen, 1996 [44]; Juvonen, 1999 [45] (Nutramigen, Mead Johnson)	qRCT	~43eHF; ~58 HM, ~43 CM	Sweden	Healthy term infants. Normal risk.	eHF-casein vs standard formula or human milk, from 0 to 3 days. Exclusively breast- fed thereafter.	0.17, 0.33, 0.67, 2, 3,	Food Allergy (clinical symptoms), Eczema (physician assessment), Wheeze (physician assessment), Allergic Sensitisation (SPT, sIgE)
Nentwich, 2001 [46] (Beba HA, Nestlé; Hipp HA, Nutricia)	qRCT	37/36	Czech Republic	Term infants with an allergic first degree relative. High Risk.	pHF-whey (Beba HA) vs eHF-whey for a mean 240 days in the first year.	0.5, 1	Eczema (physician assessment), Allergic Sensitisation (sIgE)
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	qRCT	1737 eHF; 1789 CM; 1859 HM	Finland	Infants with formula milk before hospital discharge. Normal risk.	eHF-whey vs standard formula or human milk, from birth for mean 4 days.	2, 11.5	Food allergy - CM (food challenge), Diabetes Mellitus (clinical diagnosis)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Vandenplas,		Unclear.		Infants at risk of	Hypoallergenic		
1988 [49]	~DCT	15/60	Dalainm	allergy. ? not	formula (?pHF) vs	0.22	Alleraic Consideration (sleE CDT)
(Formula	qRCT	assessed at	Belgium	breastfed.	standard formula up	0.33	Allergic Sensitisation (sIgE, SPT)
unknown)		4 months		High Risk.	to 4 months.		

ICHPPC International Classification of Health Problems in Primary Care, RCT Randomised controlled trial, qRCT Quasi-randomised controlled trial, DD Doctor diagnosis (community), Physician assessment is assessment by study physician, SPT skin prick test, sIgE specific IgE, CM cow's milk formula, HM human milk, pHF partially hydrolysed formula, eHF-c extensively hydrolysed, casein based formula, eHF-w extensively hydrolysed, whey based formula. Nan HA, Beba HA, Good Start, and Nidal HA are the same product with different brand names. Hipp HA and Nutrilon Pepti are the same product with different brand names.

Table B. Characteristics of Included Controlled Clinical Trials.

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Akimoto, 1997 [51] (Nan HA, Nestlé)	ССТ	~35/~98	Japan	Newborn infants. Disease risk not stated	pHF-whey from birth to 6 months if needed, vs standard infant formula	0.33, 1, 1.5, 3	Eczema (questionnaire survey), Wheeze (questionnaire survey)
Han, 2003 [52] (HA21, Maeil Dairy Industry)	ССТ	~40/~40	South Korea	Healthy term infants of parents with allergic disease attending a Dairy Industry maternity school. High Risk.	pHF vs standard formula from birth to 6 months as needed.	0.5	Eczema
Willems, 1993 [50] (Nan HA, Nestlé)	ССТ	~90/~90	Belgium	Infants who were not breastfed, with first degree relative affected by allergy. High Risk.	pHF-whey vs standard formula, from birth to 3 months.	1	Eczema (DD), Wheeze (DD), Allergic Rhinoconjunctivitis (DD)

CCT Controlled Clinical Trial, DD Doctor diagnosis (community), pHF partially hydrolysed formula.

Table C. Risk of Bias and Generalisability/Study Conduct Issues in Included Trials Reporting Allergic Outcomes.

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Becker, 2004 [3]; Chan-Yeung, 2000 [4]; Chan-Yeung 2005 [5]; Wong, 2013 [6] (Good Start, Nestlé)	Low	Low	Low	Low	Low	Low uptake of hydrolysed formula in intervention group
Boyle 2015 [7] (pHF, Nutricia)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil (abstract publication only)
Chan, 2002 [8] (NanHA, Nestlé)	Unclear	Unclear	Unclear	Unclear	High formula company funded study	All infants exclusively formula fed
Chirico, 1997 [9] (Vivena HA, Plada)	Unclear	Unclear	Unclear	Unclear	Unclear	Infants who 'could not be breastfed' were randomised to different formula groups on the first day of life
de Seta, 1994 [10] (Nidina HA, Nestlé)	Unclear	Unclear	Unclear	Unclear	Unclear	Breastfeeding not mentioned – intervention group may not have been breastfed at all
Dupont, 2009 [11] (Formula unknown)	Unclear	Unclear	Unclear	Unclear	Unclear	Insufficient information to assess (abstract publication only)

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Halken, 1993 [12] (Nutramigen, Mead Johnson; Profylac, ALK)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil
Lovegrove, 1994 [14] (Peptijunior, Nutricia)	Low	Unclear	Low	Unclear	High formula company funded study and first author	Nil
Lowe, 2011 [15] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	High formula company funded study	Nil
Mallet, 1992 [16] (Pregestimil, Mead Johnson)	High non-blinded study	Unclear	Low	High	Unclear	Insufficient information to assess
Marini, 1996 [17] (Nidina HA, Nestlé)	Low	Unclear	Low	Unclear	Unclear	Infants were enrolled on day 1 of life, and over 50% of infants were exclusively formula fed from this time
Martikainen, 1996 [18]; Vaarala,1998 [19] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Moran, 1992 [20] (pHF, Mead Johnson)	Unclear	Unclear	High ~35% randomised did not contribute to outcome analysis	High	High single author, an employee of formula company	All infants exclusively formula fed
Odelram, 1996 [21] (Profylac, ALK)	Low	Unclear	High ~31% randomised did not contribute to outcome analysis	High	Low	Nil
Oldaeus,1997 [22]; Oldaeus, 1999 [23] (pHF or Nutramigen, both Mead Johnson)	Low	Unclear	Low	Unclear	Unclear	Nil
Porch, 1998 [25] (Good Start, Nestlé; Nutramigen, Mead Johnson)	Low	Unclear	Low	Unclear	High formula company funded study	Some infants were randomly assigned to a formula milk at birth, with formula delivered to their local neonatal unit

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Scalabrin, 2009 [26]; Scalabrin, 2014 [27] (pHF or Nutramigen, both Mead Johnson)	Low	Low	High ~75% randomised did not contribute to outcome analysis	High	High some authors were employees of formula company	All infants solely formula fed for at least 24 hours prior to 14 days age.
Schmitz, 1992 [28] (Nidal HA, Nestlé)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil
Schonberger, 2005 [29] (Nutrilon Pepti, Nutricia)	Unclear	Unclear	Low	Unclear	Unclear	Nil
Shao, 2006 [30] (Formula unknown)	Unclear	Unclear	Low	Unclear	Unclear	Infants were randomised to formula at birth
Tsai, 1991 [31] (NanHA, Nestlé)	Unclear	Unclear	Low	Unclear	High formula supplier funded study	All infants were exclusively formula fed

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Vandenplas 1992 [33]; Vandenplas 1995 [34] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	High formula company undertook statistical analysis	All infants were exclusively formula fed
von Berg 2003 [35], 2008 [36], 2010 [37], 2013 [38] (BebaHA, Nestlé; Nutramigen, Mead Johnson; Hipp HA, Nutricia)	Low	Low	Low	Low	Unclear	Nil
Zeiger 1989 [39], 1995 [40] (Nutramigen, Mead Johnson)	Low	Unclear	High unclear how many lost to follow up early; ~40% lost to follow up between age 4 months and 4 years	High	Unclear	Nil
Exl, 1998 [41] (Beba HA, Nestlé)	High outcome assessment unlikely to be blinded	High treatment allocated according to town of birth	Low	High	High formula company funded study and employed most of the authors	Nil

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Halken, 2000 [42] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	Unclear	Nil
Juvonen, 1994 [43]; Juvonen, 1996 [44]; Juvonen, 1999 [45] (Nutramigen, Mead Johnson)	Unclear	High treatment allocated by maternal date of birth	Low	High	Low	Breastmilk was withheld for the first 3 days of life in some infants
Nentwich, 2001 [46] (Beba HA, Nestlé; Hipp HA, Nutricia)	Low	Unclear	Low	Unclear	Low	Treatment allocation during pregnancy, and participants were told the name of their allocated formula before birth
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	Unclear	Unclear	Low	Unclear	Low	87% of infants received supplementary feeding during their postnatal hospital stay (mean 4 days)
Vandenplas, 1988 [49] (Formula unknown)	Unclear	High inclusion was chronological	High number randomised not stated, but expected to be high	High	Unclear	All infants were exclusively formula fed from birth

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Akimoto, 1997 [51] (Nan HA, Nestlé)	Unclear	High no information about method of treatment allocation	High 16 participants allocated to pHF were analysed in the control group due to poor compliance	High	Unclear	Breastfeeding not mentioned – intervention group may not have been breastfed at all
Han, 2003 [52] (HA21, Maeil Dairy Industry)	Unclear	High treatment allocated according to parental preference	High ~40% randomised did not contribute to outcome analysis	High	High formula company provided 'assistance to the survey'	Nil
Willems, 1993 [50] (Nan HA, Nestlé)	Unclear	High treatment allocated according to month of birth	High ~75% randomised did not contribute to outcome analysis	High	Unclear	All infants were exclusively formula fed from birth

Nan HA, Beba HA, Good Start, and Nidal HA are the same product with different brand names. Hipp HA and Nutrilon Pepti are the same product with different brand names. Explanations are provided where judgements were made that risk of bias or conflict of interest is High.

Table D. Risk of Bias and Generalisability/Study Conduct Issues in Included Trials Reporting Autoimmune Outcomes.

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Akerblom, 2005 [1] Knip, 2010 [2] (Nutramigen, Mead Johnson)	Low	Unclear	Low	Unclear	Low	Nil
Knip, 2014 [13] (Nutramigen, Mead Johnson)	Low	Low	Low	Low	Low	Nil
Martikainen, 1996 [18]; Vaarala,1998 [19] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil
Paronen, 2000 [24] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil
Vaarala, 2012 [32] (Peptidi-Tutteli, Valio)	Unclear	Unclear	Low	Unclear	High some authors were employees of formula company	Nil
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	Unclear	Unclear	Low	Unclear	Low	87% of infants received supplementary feeding during their postnatal hospital stay (mean 4 days)

Explanations are provided where judgements were made that risk of bias or conflict of interest is High.

## References

- 1. Akerblom HK, Virtanen SM, Ilonen J, et al. Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: A pilot study. Diabetologia 2005;**48**(5):829-37
- 2. Knip M, Virtanen SM, Seppa K, et al. Dietary Intervention in Infancy and Later Signs of Beta-Cell Autoimmunity. N Engl J Med 2010;**363**(20):1900-08 doi: 10.1056/NEJMoa1004809[published Online First: Epub Date]|.
- 3. Becker A, Watson W, Ferguson A, et al. The Canadian asthma primary prevention study: outcomes at 2 years of age. J Allergy Clin Immunol 2004;**113**(4):650-6
- 4. Chan-Yeung M, Manfreda J, Dimich-Ward H, et al. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Arch Pediatr Adol Med 2000;**154**(7):657-63
- 5. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. J Allergy Clin Immunol 2005;**116**(1):49-55
- 6. Wong T, Chan-Yeung M, Rousseau R, et al. Delayed introduction of food and effect on incidence of food allergy in a population at high risk for atopy: The Canadian asthma primary prevention study (CAPPS). J J Allergy Clin Immunol 2013;1):AB96
- 7. Boyle RJ, Brown N, Chiang WC, et al. Partially hydrolysed prebiotic supplemented whey formula for the prevention of allergic manifestations in high risk infants: a multicentre double blind randomised controlled trial. Clin Trans Allergy 2015;5(Suppl 3):P30
- 8. Chan YH, Shek LP, Aw M, et al. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Pediatr Child Health 2002;**38**(1):84-8
- 9. Chirico G, Gasparoni A, Ciardelli L, et al. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. Allergy 1997;**52**(1):82-88 doi: 10.1111/j.1398-9995.1997.tb02549.x[published Online First: Epub Date]|.

- 10. de Seta L, Siani P, Cirillo G, et al. [The prevention of allergic diseases with a hypoallergenic formula: a follow-up at 24 months. The preliminary results]. Pediatria Medica e Chirurgica 1994;**16**(3):251-4
- 11. Dupont C, Basuyau J, Soulaine P, et al. Breast-milk, partially hydrolyzed formula, and extensively hydrolyzed formula: Immediate and long-term effects in infants at risk of allergy. Allergy 2009;**64**:63

  12. Halken S, Host A, Hansen LG, et al. Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study. Pediatr Allergy Immunol 1993;**4**(4):173-81
- 13. Knip M, Akerblom HK, Becker D, et al. Hydrolyzed infant formula and early beta-cell autoimmunity: a randomized clinical trial. JAMA 2014;**311**(22):2279-87 doi: http://dx.doi.org/10.1001/jama.2014.5610[published Online First: Epub Date]].
- 14. Lovegrove JA, Hampton SM, Morgan JB. The immunological and long-term atopic outcome of infants born to women following a milk-free diet during late pregnancy and lactation: a pilot study. Brit J Nutr 1994;**71**(2):223-38
- 15. Lowe AJ, Hosking CS, Bennett CM, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. J Allergy Clin Immunol 2011;**128**(2):360-65.e4
- 16. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. J Pediatr 1992;**121**(5 Pt 2):S95-100
- 17. Marini A, Agosti M, Motta G, et al. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. Acta Paediatrica Suppl 1996;414:1-21
- 18. Martikainen A, Saukkonen T, Kuimala PK, et al. Disease-associated antibodies in offspring of mothers with IDDM. Diabetes 1996;**45**(12):1706-10

- 19. Vaarala O, Paronen J, Otonkoski T, et al. Cow milk feeding induces antibodies to insulin in children A link between cow milk and insulin-dependent diabetes mellitus? Scand J Immunol 1998;47(2):131-35
- 20. Moran JR. Effects of prolonged exposure to partially hydrolyzed milk protein. J Pediatr 1992;**121**(5 Pt 2):S90-4
- 21. Odelram H, Vanto T, Jacobsen L, et al. Whey hydrolysate compared with cow's milk-based formula for weaning at about 6 months of age in high allergy-risk infants: effects on atopic disease and sensitization. Allergy 1996;**51**(3):192-5
- 22. Oldaeus G, Anjou K, Bjorksten B, et al. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. Arch Dis Child 1997;**77**(1):4-10
- 23. Oldaeus G, Bjorksten B, Jenmalm MC, et al. Cow's milk IgE and IgG antibody responses to cow's milk formulas. Allergy 1999;**54**(4):352-7
- 24. Paronen J, Knip M, Savilahti E, et al. Effect of cow's milk exposure and maternal type 1 diabetes on cellular and humoral immunization to dietary insulin in infants at genetic risk for type 1 diabetes. Finnish Trial to Reduce IDDM in the Genetically at Risk Study Group. Diabetes 2000;49(10):1657-65 25. Porch MC, Shahane AD, Leiva LE, et al. Influence of breast milk, soy or two hydrolyzed formulas on the development of allergic manifestations in infants at risk. Nutr Res 1998;18(8):1413-24 26. Scalabrin DM, Johnston WH, Hoffman DR, et al. Growth and tolerance of healthy term infants receiving hydrolyzed infant formulas supplemented with Lactobacillus rhamnosus GG: randomized, double-blind, controlled trial. Clin Pediatr 2009;48(7):734-44
- 27. Scalabrin DMF, Harris C, Strong PV, et al. Infant supplementation with Lactobacillus rhamnosus GG (LGG) and long-term growth and health: A 5-year follow-up. Allergy 2014;**69**:196-97 doi: <a href="http://dx.doi.org/10.1111/all.12493[published">http://dx.doi.org/10.1111/all.12493[published</a> Online First: Epub Date].
- 28. Schmitz J, Digeon B, Chastang C, et al. Effects of brief early exposure to partially hydrolyzed and whole cow milk proteins. J Pediatr 1992;**121**(5 II SUPPL.):S85-S89

- 29. Schonberger HJAM, Dompeling E, Knottnerus JA, et al. The PREVASC study: The clinical effect of a multifaceted educational intervention to prevent childhood asthma. Eur Resp J 2005;**25**(4):660-70
- 30. Shao J, Sheng J, Dong W, et al. [Effects of feeding intervention on development of eczema in atopy high-risk infants: an 18-month follow-up study]. Zhonghua Erke Zazhi 2006;44(9):684-7
- 31. Tsai YT, Chou CC, Hsieh KH. The effect of hypoallergenic formula on the occurrence of allergic diseases in high risk infants. Chung-Hua Min Kuo Hsiao Erh Ko i Hsueh Hui Tsa Chih 1991;32(3):137-44
- 32. Vaarala O, Ilonen J, Ruohtula T, et al. Removal of Bovine Insulin From Cow's Milk Formula and Early Initiation of Beta-Cell Autoimmunity in the FINDIA Pilot Study. Arch Pediatr Adol Med 2012;**166**(7):608-14
- 33. Vandenplas Y. Atopy at 3 years in high-risk infants fed whey hydrolysate or conventional formula. Lancet 1992;**339**(8801):1118
- 34. Vandenplas Y, Hauser B, Borre C, et al. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995; 154(6).

http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/103/CN-00118103/frame.html.

- 35. von Berg A, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;**111**(3):533-40
- 36. Berg A, Filipiak-Pittroff B, Krämer U, et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). J Allergy Clin Immunol 2008; 121(6). <a href="http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/168/CN-00640168/frame.html">http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/168/CN-00640168/frame.html</a>.
- 37. Berg A, Krämer U, Link E, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course the GINIplus study up to the age of 6

years. Clin Exp Allergy 2010; 40(4).

http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/291/CN-00750291/frame.html.

- 38. Von Berg A, Filipiak-Pittroff B, Kramer U, et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;**131**(6):1565-73.e5
- 39. Zeiger RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. J Allergy Clin Immunol 1989;84(1):72-89
- 40. Zeiger RS. Dietary manipulations in infants and their mothers and the natural course of atopic disease. Pediatr Allergy Immunol 1994;5(6 Suppl):33-43
- 41. Exl BM, Deland U, Wall M, et al. Zug-Frauenfeld nutritional survey ('Zuff Study'): Allergen-reduced nutrition in a normal infant population and its health-related effects: Results at the age of six months.

  Nutr Res 1998;18(8):1443-62
- 42. Halken S, Hansen KS, Jacobsen HP, et al. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective, randomized study. Pediatr Allergy Immunol 2000;**11**(3):149-61
- 43. Juvonen P, Mansson M, Jakobsson I. Does early diet have an effect on subsequent macromolecular absorption and serum IgE? J Pediatr Gastro Nutr 1994;**18**(3):344-9
- 44. Juvonen P, Mansson M, Andersson C, et al. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life. A three-year prospective follow-up. Acta Paediatrica 1996;85(9):1047-52
- 45. Juvonen P, Mansson M, Kjellman NI, et al. Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins. Pediatr Allergy Immunol 1999;**10**(3):191-8

- 46. Nentwich I, Michkova E, Nevoral J, et al. Cow's milk-specific cellular and humoral immune responses and atopy skin symptoms in infants from atopic families fed a partially (pHF) or extensively (eHF) hydrolyzed infant formula. Allergy 2001;56(12):1144-56
- 47. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants. Journal of Allergy & Clinical Immunology 1999;**104**(2 Pt 1):457-61
- 48. Savilahti E, Saarinen KM. Early infant feeding and type 1 diabetes. Eur J Nutr 2009;**48**(4):243-9 49. Vandenplas Y, Deneyer M, Sacre L, et al. Preliminary data on a field study with a new hypo-

allergic formula. European Journal of Pediatrics 1988;148(3):274-7

- 50. Willems R, Duchateau J, Magrez P, et al. Influence of hypoallergenic milk formula on the incidence of early allergic manifestations in infants predisposed to atopic diseases. Ann Allergy 1993;**71**(2):147-50
- 51. Akimoto K, Saito H, Akasawa A, et al. [Preventative effect of a whey hydrolyzed formula (Nestle, NAN H.A.) on the development of allergic symptoms in infants]. Arerugi 1997;**46**(10):1044-51 52. Han YS, Park HY, Ahn KM, et al. Short-term effect of partially hydrolyzed formula on the prevention of development of atopic dermatitis in infants at high risk. J Kor Med Sci 2003;**18**(4):547-51